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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/530,061	09/01/00	NOTOMI T	201487/1020

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1655	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/530,061	Notomi et al.
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- *If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.*
- *If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.*
- *Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).*
- *Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).*

Status

1) ☒ *Responsive to communication(s) filed on Aug 16, 2001 .*

2a) ☒ *This action is* **FINAL.** 2b) ☐ *This action is non-final.*

3) ☐ *Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.*

Disposition of Claims

4) ☒ *Claim(s) 29-50 is/are pending in the application.*

4a) *Of the above, claim(s) _____ is/are withdrawn from consideration.*

5) ☐ *Claim(s) _____ is/are allowed.*

6) ☒ *Claim(s) 29-50 is/are rejected.*

7) ☐ *Claim(s) _____ is/are objected to.*

8) ☐ *Claims _____ are subject to restriction and/or election requirement.*

Application Papers

9) ☐ *The specification is objected to by the Examiner.*

10) ☐ *The drawing(s) filed on _____ is/are objected to by the Examiner.*

11) ☐ *The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.*

12) ☐ *The oath or declaration is objected to by the Examiner.*

Priority under 35 U.S.C. § 119

13) ☐ *Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).*

a) ☐ *All* b) ☐ *Some** c) ☐ *None of:*

1. ☐ *Certified copies of the priority documents have been received.*
2. ☐ *Certified copies of the priority documents have been received in Application No. _____ .*
3. ☐ *Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).*

**See the attached detailed Office action for a list of the certified copies not received.*

14) ☐ *Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).*

Attachment(s)

15) ☐ *Notice of References Cited (PTO-892)*

16) ☐ *Notice of Draftsperson's Patent Drawing Review (PTO-948)*

17) ☒ *Information Disclosure Statement(s) (PTO-1449) Paper No(s). 11*

18) ☐ *Interview Summary (PTO-413) Paper No(s). _____*

19) ☐ *Notice of Informal Patent Application (PTO-152)*

20) ☐ *Other:*

DETAILED ACTION

Specification

1. Claims 1-11 and 13-28 have been canceled without prejudice towards further prosecution. New claims 29-50 have been added.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 29-50 are rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 29, the preamble of the instantly claimed method is drawn to a method of amplifying a nucleic acid while the final process step is that of displacing the second template from the first template and it is thus unclear as to whether the instantly claimed method is drawn to a method of amplifying a nucleic acid or rather displacing the second template from the first template. Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble.

Claim 29 lacks such a last step and is confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d1011, p.1011

(Bd. Pat. Applicant. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 29-41 and 45-50 are rejected under 35 U.S.C. 103(a) over Cleuziat et al. (U.S. Patent 5,874,260) (February 23, 1999) in view of Western et al. (U.S. Patent 5,612,199) (March 18, 1997).

Cleuziat et al teach a method of synthesizing nucleic acid having complementary nucleotides sequences linked alternately in a single-stranded chain (Figure 4B), comprising :

a) providing a first template having a 5' end portion comprising a second region and a second complementary region which, under suitable conditions, anneal to one another to form a loop, and a single-stranded target region connecting the 3' end portion and the 5' end portion (Example 4, Figures 1-4);

b) synthesizing a nucleic acid chain complementary to the single-stranded target region using the 3' terminal of the first template, when the first region and first complementary region are annealed to one another, as the origin of the synthesizing (Figures 2-4),

c) annealing to the first loop of the first template an oligonucleotide primer comprising at the 3' terminal a nucleotide sequence complementary to the first loop (Example 4, column 24, lines 26-42 and Figure 4B), and

d) extending the oligonucleotide primer along the first template, by means of a polymerase having strand displacement activity, to form a second template complementary to the first template, thereby displacing the first region from the first complementary and displacing the nucleic acid chain formed during the synthesizing from the first template (Figure 4B).

e) displacing the second template from the first template and the third template from the second template (Figure 4B).

Cleuziat et al teach a method wherein the 5' terminal of the oligonucleotide primer in annealing step comprises a nucleotide sequence complementary to the first region of the first template (Figures 1-4).

Cleuziat et al inherently teach the method of repeating steps B) through I) using the third template to form a fourth template which is substantially the same as the second template and a fifth template which is substantially the same as the first and third templates (Figure 4B).

Cleuziat et al teach a method, wherein the synthesizing in step B) comprises: B1) extending the 3' terminal of the first template by means of a polymerase having strand displacement activity to form the nucleic acid chain and the third loop (Figures 2- 4B).

Cleuziat et al teach the method of amplifying nucleic acid by repeating the annealing, extending and displacing steps (Figure 4B and 5).

Cleuziat et al teach the method of detecting a target nucleotide sequence in a sample, which comprises performing an amplification method and observing , whether hybridization occurs between the probes and the products of the method of amplifying (Example 2, Example 9 and Figure 9 and Example 10 and Figure 10).

Cleuziat et al teach the method wherein a probe containing a nucleotide sequence complementary to the loop is added to the amplification reaction product and hybridization therebetween is observed (Example 10, Column 32, lines 2-5).

Cleuziat et al teach the method wherein the probe is labeled and aggregation reaction occurring upon hybridization is observed (Example 11).

Cleuziat et al teach the method wherein the determining comprises detecting a change in a signal of the detector (Example 2).

Cleuziat et al do not teach the method of providing a first template having a 3' end portion comprising a first region and a first complementary region, which, under suitable conditions, anneal to one another to form a first loop.

Western et al. teach the method of providing a first template having a 3' end portion comprising a first region and a first complementary region, which, under suitable conditions, anneal to one another to form a first loop (Figure 5 and Column 14, lines 36-44 and Claims 5 and 18).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method of providing a first template having a 3' end portion comprising a first region and a first complementary region, which, under suitable conditions, anneal to one another to form a first loop of Western et al. in the method of strand displacement amplification reaction of Cleuziat et al. since Western et al. state, "The present method provides a highly convenient method for converting a polynucleotide sequence of interest to a target polynucleotide sequence having intra molecularly base-paired structure while minimizing the number of reagents and steps required (Column 8, lines 2-6) ." An ordinary practitioner would have been motivated to combine and substitute the method of providing a first template having a 3' end portion comprising a first region and a first complementary region, which, under suitable conditions, anneal to one another to form a first loop of Western et al. in the method of strand displacement amplification reaction of Cleuziat et al, in order to achieve the

express advantage, as noted by Western et al, of a method that provides a highly convenient method for converting a polynucleotide sequence of interest to a target polynucleotide sequence having intra molecularly base-paired structure while minimizing the number of reagents and steps required.

6. Claims 29-50 are rejected under 35 U.S.C. 103 (a) over Cleuziat et al. (U.S. Patent 5,874,260) (February 23, 1999) in view of Western et al. (U.S. Patent 5,612,199) (March 18, 1997). further in view of Yager et al. (U.S. Patent 6,025,139) (February 15, 2000).

Cleuziat et al. in view of Western et al. teach the method and oligonucleotides of claims 29-41 and 45-50 as described above.

Cleuziat et al in view of Western et al. do not teach the method wherein the nucleotide synthesis is carried out in the presence of a melting temperature regulator betaine at a concentration of 0.2 to 3.0M.

Yager et al teach the method wherein the nucleotide synthesis is carried out in the presence of a melting temperature regulator betaine at a concentration of 5M (Column 7, lines 49-52).

However, it is *prima facie* obvious that selection of the concentration of melting temperature regulator betaine represents routine optimization with regard to the G-C and A-T content of a particular nucleotide used in the amplification and hybridization reaction which

routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the concentration of melting temperature regulator betaine selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the melting temperature regulator betaine of Yager et al. in the method of strand displacement amplification reaction of Cleuziat et al.in view of Western et al. since Yager states, "Alternatively, an isostabilizing solvent, such as 5M betaine, could be used to eliminate the differences in melting temperature between A:T and G:C base pairs (column 7, lines 49-52)." An ordinary practitioner would have been motivated to combine and substitute the melting temperature regulator betaine of Yager et al. in the method of strand displacement amplification reaction of Cleuziat et al.in view of Western et al. , in order to achieve the express advantage, as noted by Yager et al, of an isostabilizing solvent betaine which could be used to eliminate the differences in melting temperature between A:T and G:C base pairs.

Response to Amendment

7. In response to the amendment filed on August 16, 2001, all 112 (second paragraph) rejections and 102(e) rejections are withdrawn. However, a new 112 (second paragraph) rejection and two new 103(a) rejections have been included.

Response to Arguments

8. Applicant's arguments with respect to all pending claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti , Ph. D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Arun Chakrabarti,

Patent Examiner

August 30, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

9/6/01